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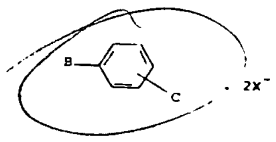
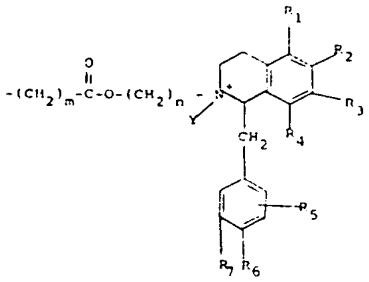
(54) NEUROMUSCULAR BLOCKING AGENTS

(57) Short acting reversible neuromuscular blocking agents of the formula:



(I)

where B and C are *para* or preferably *meta*, and each is



where m is 2, 3 or 4 and is preferably 2, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are the same or different and are hydrogen or alkoxy of 1 to 4 carbon atoms, Y is alkyl of 1 to 4 carbon atoms, n is 2, 3 or 4, most preferably 3, provided that at least one of R_1 to R_4 and one of R_5 to R_7 is lower alkoxy, and X is a pharmaceutically acceptable anion are useful upon administration to a patient in providing muscular relaxation in the patient during surgery and are normally intravenously administered in a pharmaceutically acceptable carrier.

SPECIFICATION

NEUROMUSCULAR BLOCKING AGENTS

Background of the Disclosure

In anaesthesia, neuromuscular blocking agents are used to provide skeletal muscular relaxation during surgery and during intubation of the trachea.

In general there are two types of neuromuscular blocking agents in use, non-depolarizing and depolarizing.

The non-depolarizing agents include d-tubocurarine, pancuronium, gallamine, diallyltoxiferine and toxiferine.

The depolarizing agents include succinylcholine and decamethonium. All of the conventional nondepolarizing agents when used for producing skeletal muscle relaxation in surgery have a long duration of action e.g., 60 to 180 minutes in man.

The depolarizing agents on the other hand provide muscle relaxation at dosages normally used for surgery which is less than the duration of action of non-depolarizing agents.

For example, succinylcholine provides a short duration of action of about 5 to 15 minutes whereas decamethonium provides about 20 to 40 minutes duration of muscle relaxation.

To the best of applicant's knowledge, there are no non-depolarizing agents currently available for approved clinical use which have a short duration of action.

As used herein a short duration of action is defined as less than about 10 minutes in the monkey.

The long duration of action of non-depolarizing agents is unacceptable in many surgical procedures which take less than one hour because the patient is not generally fully recovered from their effects, e.g., the patient may be unable to breathe adequately on his or her own.

Each non-depolarizing agent has inherent side-effects. For example, gallamine and pancuronium may cause tachycardia, and d-tubocurarine and diallyltoxiferine may cause hypotension.

While drugs can be pharmacologically antagonized with anticholinesterase agents, this obviously necessitates the administration of a second drug which itself may have its own side effects, e.g., bradycardia, gut spasm and bronchorrhea. Thus, to overcome the aforementioned side effects of the anticholinesterase agents, a third drug, an anticholinergic drug e.g., atropine must also be given.

The depolarizing agents to the best of applicant's knowledge have no pharmacologic antagonists. While in most cases there is no need to reverse the effects of the depolarizing agents, in certain patients the effects of succinylcholine are much prolonged because of abnormal metabolism of the agent by the patient.

The depolarizing agents due to that mode of action which initially causes skeletal muscle contraction and stimulation of smooth muscles are also known to cause the following side effects in certain instances: increased intraocular, and intragastric tension, cardiac arrhythmias, potassium release, and muscle pain.

These side effects caused by the depolarizing agents are not caused by the non-depolarizing agents. It is therefore clearly evident that a new neuromuscular blocking agent is needed which would combine the short duration of action of the depolarizing agents with the relatively few side effects and the reversibility of the non-depolarizing agents.

It should be understood that while non-depolarizing agents generally have few side effects, gallamine and pancuronium may cause tachycardia and d-tubocurarine and diallyltoxiferine may cause hypotension.

Surprisingly, the compounds of the present invention also appear to be free of these side effects at the dosages anticipated being used clinically in tests made to date. Reference may be had to the text of: The Pharmacological Basis of Therapeutics—Fifth Edition, edited by Louis S. Goodman and Alfred Gilman published by The McMillan Co., copyright 1975, Chapter 28, author George B. Koelle, for further description of neuromuscular blocking agents.

Reference should also be had to the following articles:

Neuromuscular Blocking Activity of a New Series of Quaternary N-Substituted Choline Esters—British Journal of Pharmacology, September, 1971, vol. 43, No. 1, p. 107;

The Pharmacology of New Short Acting Non-depolarizing Ester Neuromuscular Blocking Agents: Clinical Implications—published in Anaesthesia and Analgesia. . . Current Researches, Vol. 52, No. 6, p. 982, Nov.-Dec., 1973;

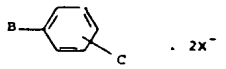
Potential Clinical Uses of Short-Acting Non-depolarizing Neuromuscular-Blocking Agents as Predicted from Animal Experiments—published in Anaesthesia and Analgesia. . . Current Researches, Vol. 54, No. 5, p. 669, Sept.-Oct., 1974; and

U.S. Patent No. 3,419,099, for a further description of neuromuscular blocking agents.

Brief Description of the Disclosure

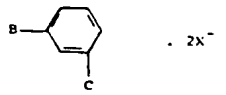
The present invention provides new neuromuscular blocking agents, sometimes called muscle relaxants, which combine a non-depolarizing mode of action with the short duration of action and reversibility needed to meet ideal clinical requirements for use during surgery.

The neuromuscular blocking agents of this invention are represented by the formula (I)



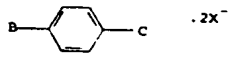
(I)

where C is most preferably *meta* to B as in formula (II)



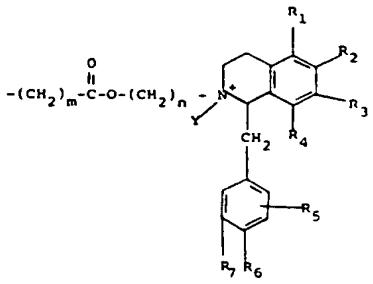
(II)

or C is *para* to B as in formula III



(III)

and where B and C are each



where m is 2, 3 or 4, and is preferably 2, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are the same or different and are hydrogen or alkoxy of 1 to 4 carbon atoms (methoxy, ethoxy, propoxy or butoxy), Y is alkyl of 1 to 4 carbon atoms (methyl, ethyl, propyl or butyl), n is 2, 3 or 4, most preferably 3, and X is a pharmaceutically acceptable anion, provided that at least one of R_1 to R_4 is always lower alkoxy and at least one of R_5 to R_7 is always lower alkoxy. The preferred compounds of this invention are those in which R_5 to R_7 are each lower alkoxy.

Of the compounds of the invention, the most preferred are the compounds of formula II or III where Y is methyl, m is 2, n is 3, R_5, R_6 and R_7 are methoxy at the 3, 4 and 5 positions of the phenyl portion of the benzyl group, R_1 to R_4 are hydrogen and R_2 and R_3 are methoxy since these compounds appear to be less quickly hydrolyzed than the dimethoxy benzyl compounds and the meta compound (formula II) is even more preferred than the corresponding para compound because it is significantly shorter acting. The most preferred compounds also exhibit minimal side effects and high potency.

Of the anions of the invention, the following are examples of those which are suitable: iodide, mesylate, tosylate, bromide, chloride, sulphate, phosphate, hydrogen phosphate, acetate, benzene sulphonate, nitrobenzene sulphonate, naphthylene sulphonate, and propionate. The mesylate and chloride cations are most preferred because of the solubility of the salt made therefrom in water. Since the activity is in the cation portion of the compound, the nature of the anion is unimportant as long as it is pharmaceutically acceptable.

The compounds of formula I, II or III are used as neuromuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration, e.g. intramuscular or intravenous administration in solution. The compounds of the present invention shown in formula I, II or III are administered to patients such as monkeys and man (humans) and other mammals to achieve a neuromuscular block. The dosage for each type of patient will vary because of the peculiarities of the species. However, a suitable intravenous amount or dosage of the compounds of formula I, II or III for monkeys would be 1.0 to 4.0 mg/kg of body weight, and for a man 0.2 to 3.0 mg/kg of body weight, and most preferably 0.5 to 1.5 mg/kg of body weight, the above being based on the weight of the cation which is the active ingredient.

The dosage for intramuscular administration is two to four times the intravenous dose. The compounds of this invention would normally be readministered every 5 to 20 minutes preferably 5 to 15 minutes after initial administration or given as a continuous infusion depending upon the length of time a muscular block is desired, and as determined by the anaesthetists and surgeon in charge of the patient. The compounds of this invention are reversible using conventional anticholinesterase agents such as neostigmine and edrophonium and appear to avoid the side effects associated with the depolarizing agents.

The compounds of formula I, II or III are therefore useful for producing a short duration neuromuscular blockade, and the present invention provides a method of producing such blockade in

mammals, e.g. man, or monkeys, by intravenously injecting a dose of 0.05 to 4.0 mg/kg to the mammal.

The compounds may be presented in a pharmaceutical formulation for parenteral administration. The formulation may be an aqueous or non-aqueous solution or emulsion in a pharmaceutically acceptable liquid or mixture of liquids, which may contain bacteriostatic agents, antioxidants, buffers, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such formulations are normally presented in unit dosage forms such as ampoules or disposable injection devices, or in multidose forms such as a bottle from which the appropriate dose may be withdrawn. All such formulations should be rendered sterile.

The compounds of this invention may be presented as a powder e.g., as a unit dose in a sealed vial to which sterile water or other pharmaceutically acceptable sterile liquid vehicle may be added by a needle.

A suitable unit dose to obtain a neuromuscular block for mammals, e.g., humans or monkeys is about 10 mg to 400 mg and most preferably 50 to 300 mg.

The compounds of this invention if desired may be administered in conjunction with other non-depolarizing agents such as listed above.

Thus a suitable pharmaceutical parenteral preparation will preferably contain 10 to 400 mg of the compounds of formula I, II or III of this invention in solution.

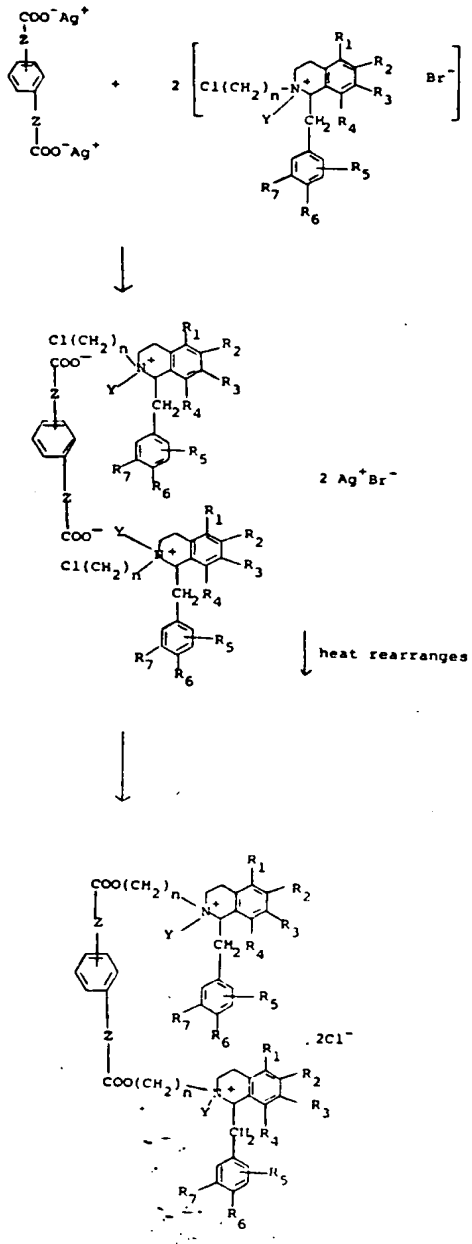
A simple and preferred formulation is a solution of the compound of formula I, II or III in water which may be prepared by simply dissolving the compound into previously sterilized pure water i.e. pyrogen free water under aseptic conditions and sterilizing the solution.

The compounds of formula I, II or III may also be administered as an infusion of a dextrose solution or a saline solution e.g., Ringers' solution.

The compounds may also be administered in other solvents such as alcohol, polyethyleneglycol and dimethylsulphoxide. They may also be administered intramuscularly as a suspension. The compounds (formula I, II or III) of this invention may be prepared by the following methods:

Method I

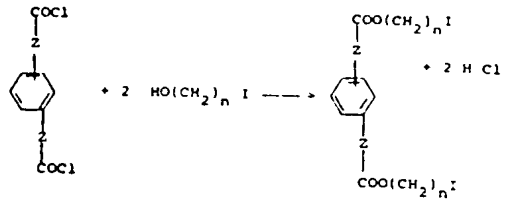
Benzyltetrahydroisoquinolines are prepared in the customary fashion from appropriately substituted phenylethylamines and phenylactic acids by the Bischler-Napieralski reaction. The tertiary benzylisoquinoline is quaternized with an appropriate α-bromo-ω-chloroalkane, α-iodo-ω-chloroalkane, or α-iodo-ω-bromoalkane. The resulting N-methyl, N-ω-haloalkyl-1-benzyltetrahydroisoquinolinium halide is boiled in water with the silver salt of the appropriate dicarboxylic acid, yielding silver bromide and the benzylisoquinolinium salt of the acid. This salt rearranges to the corresponding ester on heating: for example the generalized reaction is illustrated using α-bromo-ω-chloroalkane as follows:



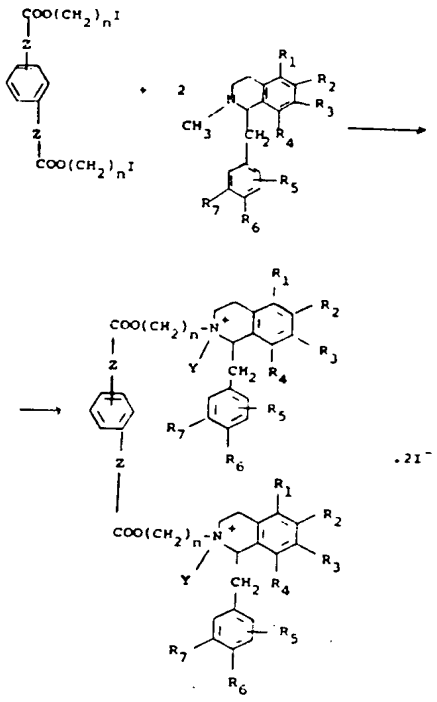
where Z is $(CH_2)_m$ and R_1 to R_7 are as defined above. Other salts are prepared by conventionally reacting the dichloro salt in an ion exchange reaction with an appropriate salt of the desired anion e.g. silver mesylate. The temperature for rearrangement is preferably 90° to 140°C.

Method 2

The bis-acid chloride of an appropriate phenylene dicarboxylic acid is prepared in the usual fashion by treatment of the acid with thionyl chloride. The acid chloride is esterified with an appropriate α-hydroxy-ω-iodoalkane, yielding the desired phenylene diacyl bis-ω-iodoalkyl ester:



The diiodoester is refluxed with an excess of e.g. two moles of an appropriate 1-benzyltetrahydroisoquinoline prepared in standard fashion by the Bischler-Napieralski reaction as described in Method 1. The desired bis-benzylisoquinoline diiode (disalt) is obtained:

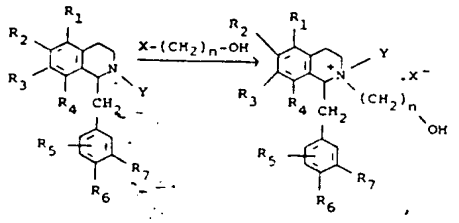


where Z is $(CH_2)_m$ and R_1 to R_7 are defined as above. The desired salts are then prepared in a conventional ion exchange reaction as described in Method 1. Bromine or chlorine may be substituted for iodine in the α-hydroxy-ω-iodoalkane if desired and the reaction run as above.

Method 3

The appropriate 1-benzyltetrahydroisoquinoline prepared as described in method 1 is quaternized with the appropriate α-halogeno-ω-hydroxyalkane.

This process may be carried out in a variety of solvents (e.g., acetonitrile, lower alcohols, DMF, aromatic hydrocarbons, etc.) over temperature ranging from ambient to reflux.



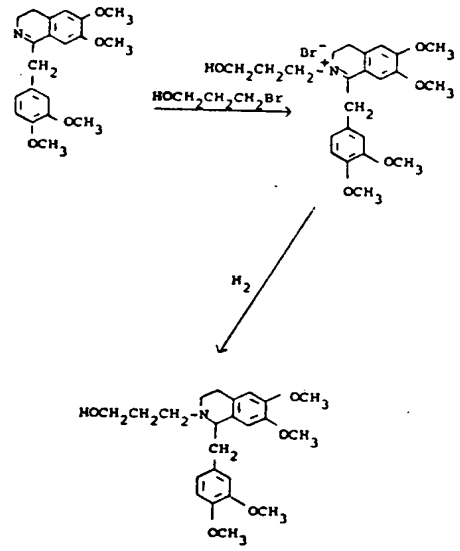
The bis acid chloride of an appropriate *meta* or *para* phenylene dicarboxylic acid is prepared in the usual fashion by treatment with a reagent such as thionyl chloride.

The bis acid chloride is then esterified with e.g., two moles of the appropriate quaternary salt containing an ω-hydroxyalkyl chain. The desired salts are then prepared by ion exchange using conventional methods such as metathesis with a silver salt, an anion exchange resin, etc.

Method 4

By an alternative method, the product of the Bischler-Napieralski reaction is quaternized with 3-bromo-1-propanol in acetone at room temperature. On reduction with Zn a tetrahydroisoquinoline is obtained containing 2-hydroxypropyl substitution. This amino alcohol is acylated with the desired acid chloride in chloroform at room temperature and then refluxed for 30 minutes. Chloroform is then evaporated *in vacuo*, the residue is slurried in water; made alkaline by adding excess K_2CO_3, and extracted with ether. Ether is evaporated and the tertiary ester is dissolved in acetone. Excess methyl iodide is added and the solution is left to stand overnight. Excess ether is added to precipitate the quaternary ester. The latter is filtered and dried.

Example (laudanosine)



tertiary "Amino Alcohol"

The tertiary amino alcohol is then conjugated with the appropriate acid chloride (obtained as described in Methods 2 or 3) under conditions described in Method 3 to yield the desired tertiary ester. This product may then be treated with an alkyl halide to yield the desired bis quaternary ester as set forth above.

m and *p*-Phenylene diacetic acids were commercially available (Aldrich). *m* and *p*-Phenylene diacrylic acids were prepared through Knoevenagel-Doebner condensation of isophthalic and terephthalic aldehydes with malonic acid. Terephthalic aldehyde (150 mM) and malonic acid (180 mM) were mixed with pyridine (45 ml) and piperidine (1.5 ml). The mixture was heated on a steam bath (85°—95°) for 3 hours. The solution was then cooled at room temperature and distilled in vacuum to remove pyridine. The solid residue was washed in hot isopropanol (70°) to remove residual pyridine. The product, *p*-phenylene diacrylic acid, was filtered and dried (M.p. >275°).

m-Phenylene diacrylic acid was prepared from isophthalaldehyde in exactly the same way. (M.p. >275°).

m and *p*-Phenylene dipropionic acids may be prepared using conventional processes by catalytic reduction, e.g., by reacting the corresponding phenylene diacrylic acid with hydrogen at 40 to 45 psi gauge pressure in the presence of 5% palladium on charcoal in dilute methanol or dimethylformamide at room temperature to 55°C. For another method, see also Wagner & Zook, Synthetic Organic Chemistrye 1973, see page 431 for method 26.

The compounds of this invention may sometimes include water of hydration in various amount e.g., 1 to 5 molecules or more of water per quaternary grouping and it is intended that this invention include such compounds containing water of hydration.

The following examples illustrate the invention. Temperatures are in degrees centigrade.

EXAMPLE 1

Preparation of Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium) propyl *m*-phenylene-3,3'-dipropionate dichloride (HH110)

1. Preparation of silver *m*-phenylene dipropionate

m-phenylene dipropionic acid 4.4 gm = 40 meq

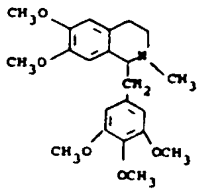
H_2O 60 ml

KOH 1N 40 ml

This mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm = 40 mM is added to the yellow hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered and the filter cake is washed with water, refiltered and dried. Yield =

quantitative. The product is an amorphous, slightly coloured powder. It is pulverised for use in the next step.

2. Preparation of 5'-Methoxylaudanosine



3,4-Dimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid are heated together at 165—190° in a flask until bubbling of water subsides. The product N-(3,4,5-trimethoxyphenylacetyl) homoveratrylamine, is recrystallized from methanol. Yield = 80%. M.p. = 94°.

3.9 gm (10 mM) N-(3,4,5-trimethoxyphenylacetyl) homoveratrylamine is refluxed in 15 ml toluene together with 5 ml $POCl_3$ for 2 hours. The settled semisolids are carefully separated ($POCl_3$ excess!) and the free base liberated by adding excess of NaOH and extracted with benzene. The product, 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl) 3,4-dihydroisoquinoline is refluxed in acetone or benzene with an excess of methyl iodide. The quaternary salt, 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide, precipitates out. M.p. = 224°.

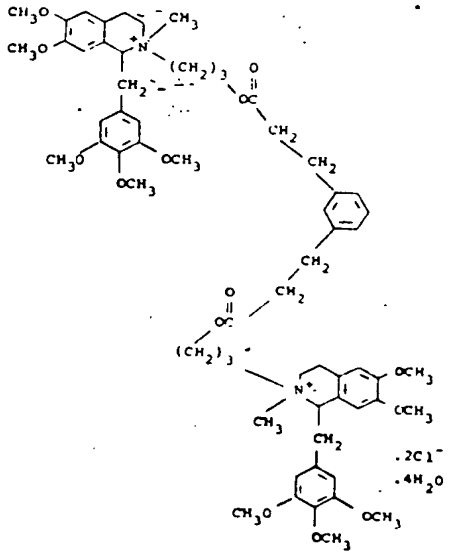
1 gm (10 mM) 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide is dissolved in 80 ml H_2O and 16 ml concentrated HCl. Zinc dust (1.1 gm) is added in small portions to the boiling stirred solution. The yellow colour disappears (reaction time 15—20 minutes). The mixture is filtered hot from some unreacted zinc and rendered alkaline with concentrated NaOH. It is impractical to filter the partly precipitated zinc hydroxide, so to avoid emulsions, the whole mixture is carefully shaken with chloroform. The residue of the chloroform solution is redissolved in ether and the ether insolubles are filtered off. The ether residue does not crystallize on standing. This amine is a gummy material which hardens on standing. The crude amine is used in the next step.

3. Preparation of N-(3-chloropropyl)-5'-methoxylaudanosinium bromide

5'-Methoxylaudanosine 1.4 gm = 4 mM is dissolved in 8 ml dimethylformamide by warming slightly. 1-Bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted 5'-methoxylaudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in either for one day, low melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

4. Preparation of *m*-phenylene dipropionic diester of N-propyl 5'-methoxylaudanosine (HH110) (Horenstein-Pahlicke Ester Formation).



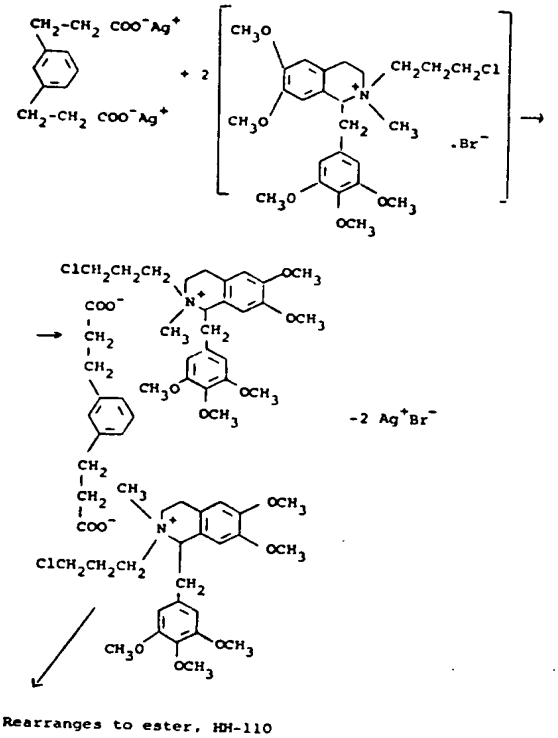
HH—110

N-(3-chloropropyl)-5'-methoxylaudanosinium bromide 2.1 gm = 4 mM

Silver *m*-phenylene dipropionate 0.85 gm = 4 mM

H_2O about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue is done for about 2 hours on a steam bath (90°C), after which rearrangement to the ester is complete:



Rearranges to ester, HH-110

The amorphous residue is boiled with isopropanol (about 40 ml) and filtered hot from some trace mechanical impurities. Gums precipitate from the filtrate at room temperature and the precipitation is completed at about −3° overnight. The supernatant is decanted and the material is slurried in ethyl acetate twice. By now the gum is semisolid and can be filtered off. After careful drying at 75° the gums become solids. At this stage they still probably retain water in varying degrees. Yield = 1.0 gm (about 40%). Yields vary from batch to batch. M.p. = 80—90° (decomposes).

Analysis %	Calculated %	Found %
C	52.99	53.22
H	6.46	5.94
N	1.99	2.00
I	18.06	19.38

calculations assume $2H_2O$ per quaternary group.

EXAMPLE 2

Preparation of Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium)-propyl *p*-phenylene-3,3'-dipropionate dichloride (HH177)

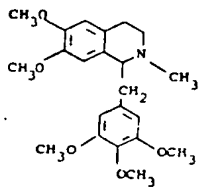
1. Preparation of silver *p*-phenylene dipropionate

p-phenylene dipropionic acid 4.4 gm = 40 meq, purchased from Aldrich

H_2O	60 ml
KOH 1N	40 ml

The mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm = 40 mM is added to the yellow hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered and the filter cake is washed with water, refiltered and dried. Yield = quantitative. The product is an amorphous, slightly coloured powder. It is pulverized for use in the next step.

2. Preparation of 5'-methoxylaudanosine

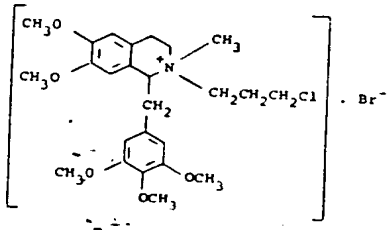


3,4-Dimethoxyphenylethylamino and 3,4,5-trimethoxyphenylacetic acid are heated together at 165—190° in a flask until bubbling of water subsides. The product, N-(3,4,5-trimethoxyphenylacetyl)-homoveratrylamine, is recrystallized from methanol. Yield = 80%. M.p. = 94°.

3.9 gm (10 mM) N-(3,4,5-trimethoxyphenylacetyl)-homoveratrylamine is refluxed in 15 ml toluene together with 5 ml $POCl_3$ for 2 hours. The settled semisolids are carefully separated ($POCl_3$ excess!) and the free base liberated by adding excess of NaOH and extracted with benzene. The product, 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl) 3,4-dihydroisoquinoline is refluxed in acetone or benzene with an excess of methyl iodide. The quaternary salt, 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide, precipitates out. M.p. = 224°.

1 gm (10 mM) 6,7-dimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide is dissolved in 80 ml H_2O and 16 ml concentrated HCl. Zinc dust (1.1 gm) is added in small portions to the boiling stirred solution. The yellow colour disappears (reaction time 15—20 minutes). The mixture is filtered hot from some unreacted zinc and rendered alkaline with concentrated NaOH. It is impractical to filter the partly precipitated zinc hydroxide, so to avoid emulsions, the whole mixture is carefully shaken with chloroform. The residue of the chloroform solution is redissolved in ether and the ether insolubles are filtered off. The ether residue does not crystallize on standing. This amine is a gummy material which hardens on standing. The crude amine is used in the next step.

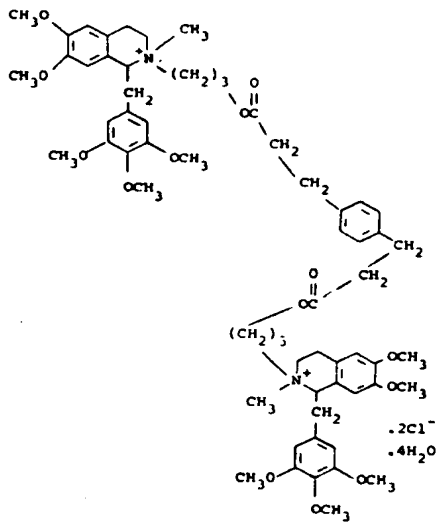
3. Preparation of N-(3-chloropropyl)-5'-methoxylaudanosinium bromide



5'-Methoxylaudanosine 1.4 gm = 4 mM is dissolved in 8 ml dimethylformamide by warming slightly. 1-Bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted laudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in ether for one day, low melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

4. Preparation of *p*-phenylene dipropionate diester of N-propyl 5'-methoxylaudanosine (HH177) (Horenstein-Pahlicke Ester Formation)



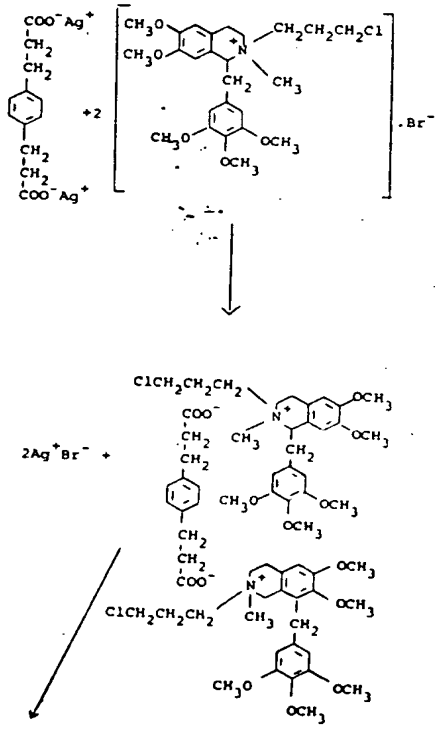
HH—177

N-(3-chloropropyl)-5'-methoxylaudanosinium bromide 2.1 gm = 4 mM

Silver *p*-phenylene dipropionate 0.85 gm = 4 mM

H_2O about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue on a steam bath (90°C) is done for about 2 hours, after which rearrangement of the ester is complete:



Rearranges to ester, HH-177

The amorphous residue is boiled with isopropanol (about 40 ml) and filtered hot from some trace mechanical impurities. Gums precipitate from the filtrate at room temperature and the precipitation is completed about −3° overnight. The supernatant is decanted and the material is slurried in ethyl acetate twice. By now the gum is semisolid and can be filtered off. After careful drying at 75° the gums become solids. At this stage they still probably retain water in varying degrees. Yield = 1.0 gm (about 40%). Yields vary from batch to batch. M.p. = 80—90% (decomposes).

EXAMPLE 3

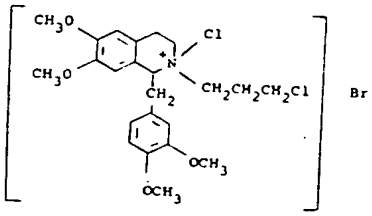
Preparation of Bis-3-[N-methyl-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *p*-phenylene-3,3'-dipropionate dichloride (HH121)

1. Preparation of silver *p*-phenylene dipropionate

p-phenylene dipropionic acid 4.4 gm = 40 meq, purchased from Aldrich	
H_2O	60 ml
KOH 1N	40 ml

The mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm = 40 mM is added to the yellow hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered and the filter cake is washed with water, refiltered and dried. Yield = quantitative. The product is an amorphous, slightly coloured powder. It is pulverized for use in the next step.

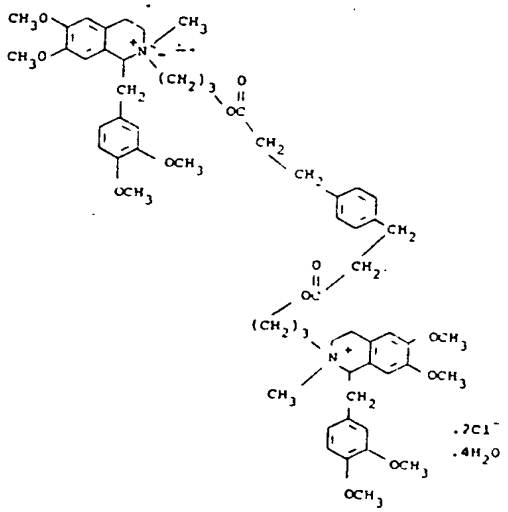
2. Preparation of N-(3-chloropropyl) laudanosinium bromide



Laudanosine (Aldrich) 1.4 gm = 4 mM is dissolved in 8 ml dimethylformamide by warming slightly. 1-Bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted laudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in ether for one day, low melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

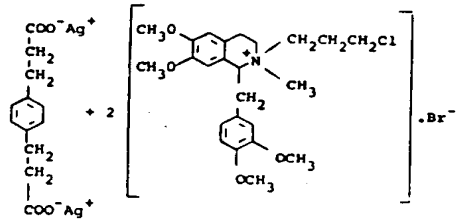
3. Preparation of *p*-phenylene dipropionic diester of N-propyl laudanosine (HH121) (Horenstein-Pahlicke Ester Formation)

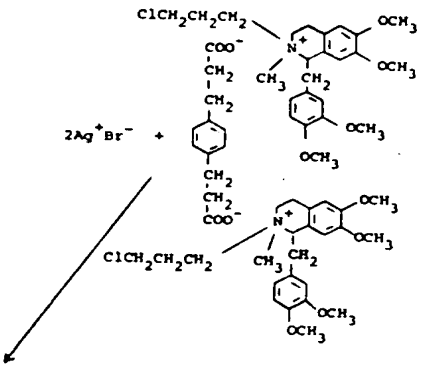


HH121

N-(3-chloropropyl) laudanosinium bromide 2.1 gm = 4 mM	
Silver *p*-phenylene dipropionate 0.85 gm = 4 mM	
H_2O	about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue is done for about 2 hours, after which the rearrangement to the ester is complete.





Rearranges to ester, HH-121

The amorphous residue is boiled to isopropanol (about 40 ml) and filtered hot from some trace mechanical impurities. Gums precipitate from the filtrate at room temperature and the precipitation is completed at about −3° overnight. The supernatant is decanted and the material is slurried in ethyl acetate twice. By now the gum is semisolid and can be filtered off. After careful drying at 75° the gums become solids. At this stage they still probably retain water in varying degrees. Yield = 1.0 gm (about 40%). Yields vary from batch to batch. M.p. = 80—90° (decomposes).

Analysis:	Calculated %	Found %
C	53.57	53.62
H	6.44	6.06
N	2.08	2.10
I	18.87	18.87

Calculations assume $2H_2O$ per quaternary group.

EXAMPLE 4

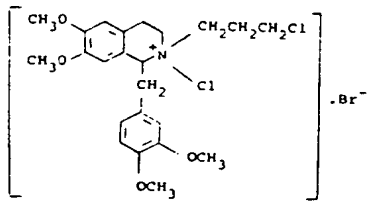
Preparation of Bis-3-[N-methyl-1-(3,4-dimethoxybenzyl) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *m*-phenylene-3,3'-dipropionate dichloride (HH35)

1. Preparation of silver *m*-phenylene dipropionate
m-phenylene dipropionic acid 4.4 gm = 40 meq,
purchased from Aldrich

H_2O	60 ml
KOH 1N	40 ml

The mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm=40 mM is added to the yellow hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered and the filter cake is washed with water, refiltered and dried. Yield = quantitative. The product is an amorphous, slightly coloured powder. It is pulverized for use in the next step.

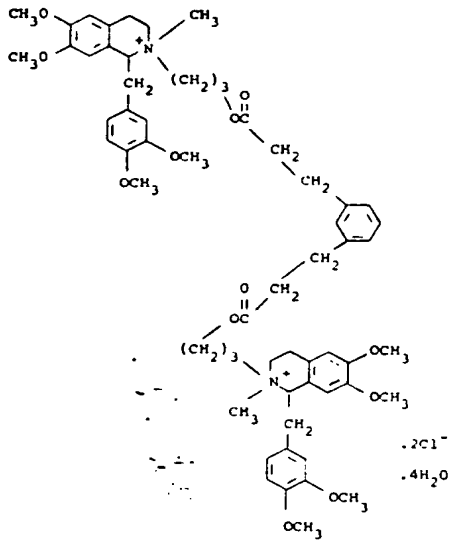
2. Preparation of 3-chloropropyl laudanosinium bromide



Laudanosine (Aldrich) 1.4 gm = 4 mM is dissolved in 8 ml dimethylformamide by warming slightly. 1-Bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted laudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in ether for one day, low-melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

3. Preparation of *m*-phenylene dipropionic diester of N-propyl laudanosine (HH35) (Horenstein-Pahlicke Ester Formation)



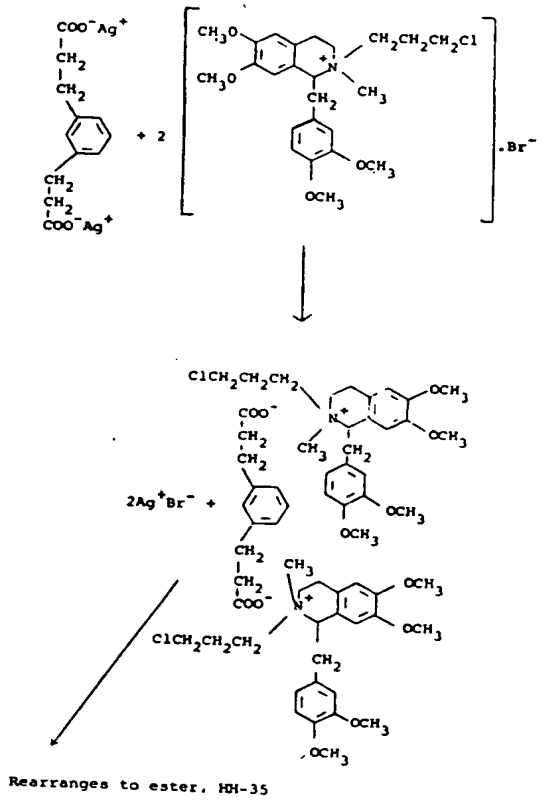
HH—35

N-(3-chloropropyl) laudanosinium bromide 2.1 gm = 4mM

Silver *m*-phenylene dipropionate 0.85 gm = 4mM

H_2O about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue is done for about 2 hours on a steam bath at 90°C, after which the rearrangement to the ester is complete:



The amorphous residue is boiled with isopropanol (about 40 ml) and filtered hot from some trace mechanical impurities. Gums precipitate from the filtrate at room temperature and the precipitation is completed at about −3° overnight. The supernatant is decanted and the material is slurried in ethyl acetate twice. By now the gum is semisolid and can be filtered off. After careful drying at 75° the gums become solids. At this stage they still probably retain water in varying degrees. Yield = 1.0 gm (about 40%). Yields vary from batch to batch. M.p. = 80—90° (decomposes).

EXAMPLE 5

Preparation of Bis-3-[N-methyl-1-(3,4-dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *p*-phenylene-3,3′-dipropionate dichloride (LL37)

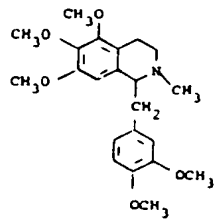
1. Preparation of silver *p*-phenylene dipropionate

p-phenylene dipropionic acid 4.4 gm = 40 meq

H_2O	60 ml
KOH 1N	40 ml

The mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm = 40 mM is added to the yellow hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered and the filter cake is washed with water, refiltered and dried. Yield = quantitative. The product is an amorphous, slightly coloured powder. It is pulverized for use in the next step.

2. Preparation of 5-methoxylaudanosine [N-methyl-1-(3,4-dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline]



2,3,4-Trimethoxyphenylethylamine and 3,4-dimethoxyphenylacetic acid are heated together at 165—190° in a flask until bubbling of water subsides. The product N-(3,4-dimethoxyphenylacetyl)-2,3,4-trimethoxyphenylethylamine, is recrystallized from methanol. Yield = 80%. M.p. = 101°.

3.9 gm (10 mM) N-(3,4-dimethoxyphenylacetyl)-2,3,4-trimethoxyphenylethylamine is refluxed in 15 ml toluene together with 5 ml $POCl_3$ for 2 hours. The settled semisolids are carefully separated ($POCl_3$ excess!) and the free base liberated by adding excess of NaOH and extracted with benzene. The product, 5,6,7,-trimethoxy-1-(3',4'-dimethoxybenzyl)-3,4-dihydroisoquinoline, is refluxed in acetone or benzene with an excess of methyl iodide. The quaternary salt, 5,6,7,-trimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide, precipitates out. M.p. = 165°.

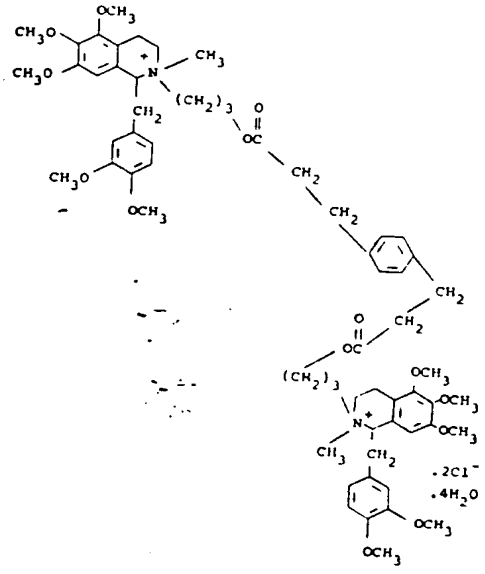
1 gm (10 mM) 5,6,7-trimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl 3,4-dihydroisoquinolinium iodide is dissolved in 80 ml H_2O and 16 ml concentrated HCl. Zinc dust (1.1 gm) is added in small portions to the boiling stirred solution. The yellow colour disappears (reaction time 15—20 minutes). The mixture is filtered hot from some unreacted zinc and rendered alkaline with concentrated NaOH. It is impractical to filter the partly precipitated zinc hydroxide, so to avoid emulsions, the whole mixture is carefully shaken with chloroform. The residue of the chloroform solution is redissolved in ether and the ether insolubles are filtered off. The ether residue does not crystallize on standing. This amine is a gummy material which hardens on standing. The crude amine is used in the next step.

3. Preparation of N-(3-chloropropyl)-5-methoxylaudanosinium bromide

5-Methoxylaudanosine 1.4 gm = 4 mM is dissolved in 8 ml dimethylformamide by warming slightly. 1-Bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted 5-methoxylaudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in ether for one day, low melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

4. Preparation of *p*-phenylene diprcpionic diester of N-propyl 5-methoxylaudanosine (LL37) (Horenstein-Pahlicke Ester Formation)



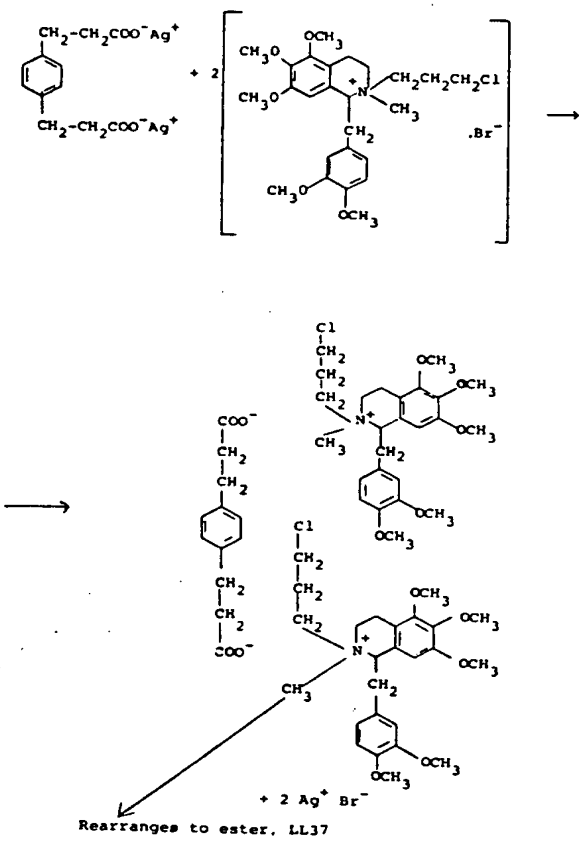
LL37

N-(3-chloropropyl)-5-methoxylaudanosinium bromide 2.1 gm = 4mM

Silver *p*-phenylene dipropionate 0.85 gm = 4 mM

H_2O about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue is done for about 2 hours on a steam bath (90°C), after which rearrangement to the ester is complete:



The amorphous residue is boiled with isopropanol (about 40 ml) and filtered hot from some trace mechanical impurities. Gums precipitate from the filtrate at room temperature and the precipitation is completed at about −3° overnight. The supernatant is decanted and the material is slurried in ethyl acetate twice. By now the gum is semisolid and can be filtered off. After careful drying at 75° the gums become solids. At this stage, they still probably retain water in varying degrees. Yield = 1.0 gm (about 40%). Yields vary from batch to batch. M.p. = 80—90° (decomposes).

EXAMPLE 6

Preparation of Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *p*-phenylene-3,3'-dipropionate dichloride (KK194)

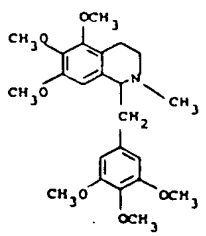
1. Preparation of silver *p*-phenylene dipropionate

p-phenylene dipropionic acid 4.4 gm = 40 mEq

H_2O	60 ml
KOH 1N	40 ml

The mixture is heated to boiling, and, if necessary, the pH is adjusted to 7.0 with the same acid. $AgNO_3$ 6.8 gm=40 mM is added to the hot solution. Immediately a heavy precipitate forms. The mixture is cooled and filtered, and the filter cake is washed with water, refiltered and dried. Yield = quantitative. The product is an amorphous, slightly coloured powder. It is pulverised for use in the next step.

2. Preparation of 5,5'-dimethoxylaudanosine



2,3,4-Dimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid are heated together at 165—190° in a flask until bubbling of water subsides. The product, N-(3,4,5,-trimethoxyphenylacetyl)-2,3,4-trimethoxyphenylethylamine, is recrystallized from methanol. Yield = 80%. M.p. = 85°.

3.9 gm (10 mM) N-(3,4,5-trimethoxyphenylacetyl)-2,3,4-trimethoxyphenylethylamine is refluxed in 15 ml toluene together with 5 ml $POCl_3$ for two hours. The settled semisolids are carefully separated ($POCl_3$ excess!) and the free base liberated by adding excess of NaOH and extracted with benzene. The product, 5,6,7-trimethoxy-1-(3',4',5'-trimethoxybenzyl)-3,4-dihydroisoquinoline, is refluxed in acetone or benzene with an excess of methyl iodide. The quaternary salt, 5,6,7-trimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl-3,4-dihydroisoquinolinium iodide, precipitates out. M.p. = 181°.

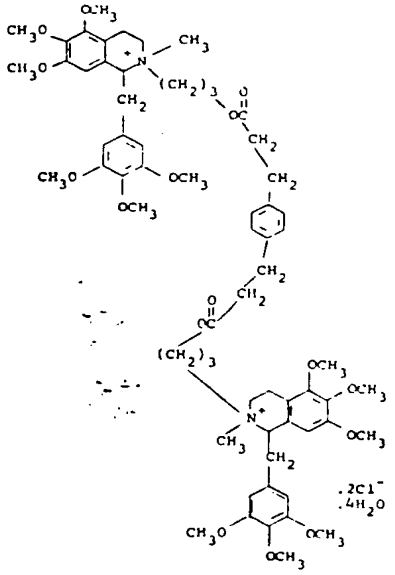
1 gm (10 mM) 5,6,7-trimethoxy-1-(3',4',5'-trimethoxybenzyl)-2-methyl-3,4-dihydroisoquinolinium iodide is dissolved in 80 ml H_2O and 16 ml concentrated HCl. Zinc dust (1.1 gm) is added in small portions to the boiling stirred solution. The yellow colour disappears (reaction time 15—20 minutes). The mixture is filtered hot from some unreacted zinc and rendered alkaline with concentrated NaOH. It is impractical to filter the partly precipitated zinc hydroxide, so to avoid emulsions, the whole mixture is carefully shaken with chloroform. The residue of the chloroform solution is redissolved in ether and the ether insolubles are filtered off. The ether residue does not crystallize on standing. This amine is a gummy material which hardens on standing. The crude amine is used in the next step.

3. Preparation of N-(3-chloropropyl)5,5'-dimethoxylaudanosinium bromide

5,5'-dimethoxylaudanosine 1.4 gm = 4 mM is dissolved in 8 ml dimethyformamide by warming slightly. 1-bromo-3-chloropropane 1.2 gm (about 100% excess) is added and the mixture is left at room temperature for 5 days. (Sometimes part of the unreacted 5,5'-dimethoxylaudanosine crystallizes out, but eventually it redissolves).

The reddish-orange solution is treated with a large amount of ether and the precipitated gummy quaternary salt is decanted and slurried in fresh ether. After standing in ether for one day, low melting solids are obtained. Yield = 1.6 gm, about 80% of theory.

4. Preparation of *p*-phenylene dipropionic diester of N-propyl 5'-methoxylaudanosine (KK194) (Horenstein-Pahlicke Ester Formation)

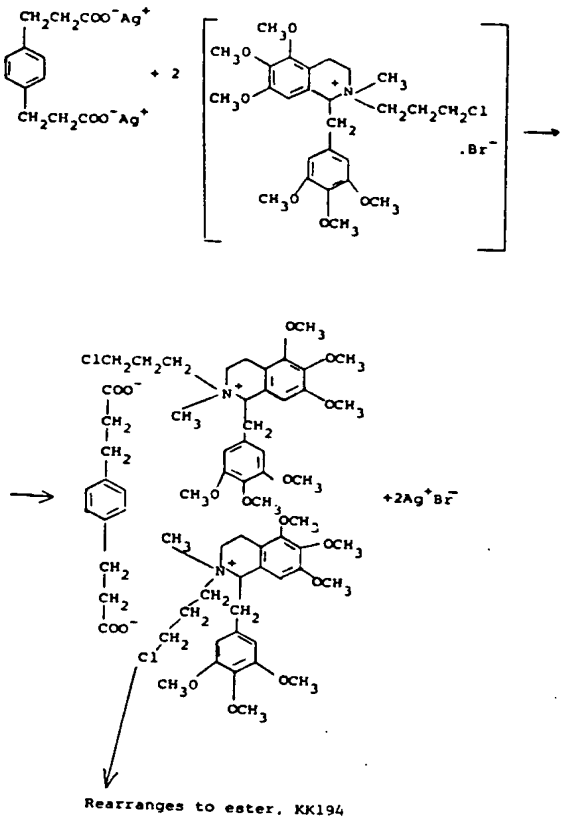


N-(3-chloropropyl)-5,5'-dimethoxylaudanosinium bromide 2.1 gm = 4 mM

Silver *p*-phenylene dipropionate 0.85 = 4 mM

H_2O about 150 ml

The mixture is boiled in an open beaker for about 10—15 minutes, stirring by hand from time to time. At the boiling temperature the silver salt is slightly soluble and reacts with the quaternary bromide. The mixture is cooled to room temperature, filtered straight and the aqueous solution is evaporated to dryness in a large dish on a steam bath. Continued heating of the residue is done for about 2 hours on a steam bath (90°C), after which rearrangement to the ester is complete:



EXAMPLE 7

Pharmaceutical formulation (HH 110) is dissolved in water for injection to a concentration of mg/ml. The solution is then poured into 20 ml vials which are then sealed.

EXAMPLE 8

Sterile (HH 110) powder (100 mg) is aseptically packaged in 20 ml vials sealed with a rubber-stopper. Ten ml sterile water for injection is added to the vials in order to produce a 1 percent (10 mg/ml) solution of (HH 110).

EXAMPLE 9

The compounds HH 110, HH 177, HH 121, and HH 35 were each separately dissolved in 0.9 percent saline at a concentration of 2 mg/ml. Cynomolgus monkeys are anaesthetised with halothane, nitrous oxide and oxygen. The maintenance concentration of halothane was 1.0%. Arterial and venous catheters were placed in the femoral vessels for drug administration and recording of the arterial pressure. Controlled ventilation was accomplished *via* an endotracheal tube. Twitch and tetanic contractions of the tibialis arterior muscle were elicited indirectly *via* the sciatic nerve. Recordings of arterial pressure electrocardiogram (lead I), heart rate and muscle function were made simultaneously.

EXAMPLE 10

Bis-3-[N-methyl-1-(3,4-trimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolimium] propyl *m*-phenylene-3,3'-dipropionate dimesylate is prepared in an ion exchange reaction by reacting HH 110 with silver mesylate. The dichloride HH 110 is dissolved in acetonitrile as is the silver mesylate. The reaction mixture is stirred at room temperature for 30 minutes to form the silver chloride precipitate. The mixture is filtered through filter paper to remove the silver chloride thereby leaving the mesylate salt in solution. The acetonitrile is then evaporated.

The product is then dissolved in ethanol and filtered to remove residual silver mesylate. The ethanol is then evaporated.

EXAMPLE 11

Preparation of bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium]-propyl *m*-phenylene-3,3'-dipropionate diiodide tetrahydrate.

N-(3-hydroxypropyl)-5'-methoxylaudanosinium iodide, 3.2 g, was dissolved in dry acetonitrile and 4 g of molecular sieve #4, was added. After stirring for 24 hours at room temperature *m*-phenylene

dipropionyl dichloride [prepared by action of thionyl chloride on the known *m*-phenylene dipropionic acid: F. S. Kipping, J. Chem. Soc., *53*, 21 (1888)], 0.78 g, was added followed by another 4 g of molecular sieve #4'. The mixture was stirred for 24—48 hours at room temperature, filtered and evaporated to dryness giving a dark brown oil which was dissolved in hot ethanol and re-precipitated as a light brown oil by cooling. The oil solidified to a light brown amorphous solid after drying. A 60% yield was obtained.

This procedure was also used to prepare related compounds by substituting *para*-phenylene dipropionyl dichloride for the *meta* isomer and N-(3-hydroxypropyl)-laudanosinium iodide for the 5'-methoxylaudanosinium iodide.

EXAMPLE 12

Preparation of N-(3-hydroxypropyl)-5'-methoxylaudanosinium iodide.

One gram of 5'-methoxylaudanosine [J. Russell Flack, L. L. Miller and F. R. Stermitz—Tetrahedron, *30*, 931 (1974)] in 20 ml of dry acetonitrile was refluxed with 1.2 g of 1-iodo-3-propanol [S. Wawzonek, J. Org. Chem., *25*, 2068 (1960)] for 24 hours. The mixture was filtered: solvent was evaporated under vacuum and ether was added to precipitate a yellow oily solid. After decanting the ether and drying at 60° a yellow powder was obtained in quantitative yield.

The same procedure was used to prepare N-(3-hydroxypropyl)-laudanosinium iodide.

EXAMPLE 13

1,2,3,4-Tetrahydroisoquinolines

These compounds were prepared by cyclodehydration of β-phenylethylamides to 3,4-dihydroisoquinolines which were quaternized with CH_3 and then reduced by Zn in hot HCl to the corresponding 1,2,3,4-tetrahydroisoquinolines.

For example, laudanosine [1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline] was prepared in the following manner: 3,4-dimethoxyphenylethylamine (Aldrich) (100 mM) was mixed with 3,4-dimethoxyphenylacetic acid (Aldrich) (100 mM) and heated at 190—200° until bubbling stops (20 minutes). The product (homoveratroylhomoveratrylamine) is cooled and recrystallized from methanol. Yield = 85%. M.p. = 122°. Homoveratroylhomoveratrylamine (100 mM) was mixed with 250 ml toluene and 50 ml $PCOl_3$ and heated to boiling for 2 hours, then cooled to room temperature. The crystalloid precipitate was filtered, rinsed with petroleum ether, dissolved in water, rendered alkaline with excess of NH_3 and extracted with benzene. The solution was then dried with sodium sulphate, filtered, and excess methyl iodide was added. The solution was refluxed for 15 minutes, and then left to stand at room temperature for twelve hours. The quaternary salt, dihydropapaverine methiodide, precipitates out. 100 mM of this quaternary salt is then reduced by boiling with 12 gm zinc dust in 600 ml water and 120 ml concentrated hydrochloric acid for one hour, and filtered hot to remove unreacted zinc. Excess ammonia is then added and the product is extracted with chloroform. The chloroform is then evaporated and the product (laudanosine) is extracted with petroleum ether, from which it crystallizes on cooling. M.p. = 114—115°.

By an analogous procedure to that described above for the synthesis of laudanosine, the corresponding benzylisoquinoline may be prepared from the analogous starting materials. For example:

3,4-dimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid (to yield 5'-methoxylaudanosine);

2,3,4-trimethoxyphenylethylamine and 3,4-dimethoxyphenylacetic acid (to yield 5-methoxylaudanosine);

3,4,5-trimethoxyphenylethylamine (mescaline) and 3,4-dimethoxyphenylacetic acid (to yield 8-methoxylaudanosine);

2,3,4-trimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid (to yield 5,5'-dimethoxylaudanosine):

3,4,5-trimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid (to yield 8,5'-dimethoxylaudanosine).

The above compounds are then reacted as in Methods 1 to 4 to prepare the compounds of this invention.

As shown in Table 1, four to six animals received each compound. Four additional animals received succinylcholine chloride or d-tubocurarine chloride as controls. The chart shows the dose range required to produce 95 percent block of the twitch response of the tibialis anterior muscle under above anaesthetic conditions in each series of animals receiving each drug. Also listed in the chart is the range of the duration of action of each compound in each series of animals. Duration of action is defined as the time span from drug injection to full recovery of the twitch response of the tibialis anterior muscle.

The duration of action of these compounds in monkeys is more indicative of the possible duration of action of the compounds in man than studies done in other species, such as the cat and dog, for the following reason: the compounds are believed to be broken down (hydrolyzed) by an enzyme (plasma cholinesterase) present in man, monkey, cat and dog. The rate of breakdown of any compound by this enzyme is believed to be the principal determinant of its duration of action in the body. The plasma cholinesterase activity of the monkey is known to be most similar to that of man ((cf. Hobbiger and Peck, British Journal of Pharmacology 37: 258—271, (1969)).

TABLE 1

Neuromuscular Blocking Potency of Selected Compounds in the Cynomolgus Monkey

Compound	Number of Animals Tested	HD_{95}* (Mg/Kg Cation)
HH 110	6	0.5 – 1.0
HH 177	4	0.5 – 1.0
HH 121	6	2.0 – 4.0
HH 35	4	2.0 – 4.0
Succinyl-choline	4	1.0 – 2.0
d-Tubo-curarine	4	0.2 – 0.4

*HD_{95} means the dose necessary to produce 95 percent block of the twitch response of the tibialis anterior muscle stimulated indirectly at 0.15 HZ *via* the sciatic nerve.

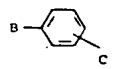
TABLE 1 (Continued)

Neuromuscular Blocking Potency of Selected Compounds in the Cynomolgus Monkey

Compound	Range of Duration of Action (Minute From Injection to Full Recovery)
HH 110	5 – 8
HH 177	8 – 12
HH 121	4 – 6
HH 35	3 – 5
Succinyl-choline	4 – 6
d-Tubo-curarine	30 – 50

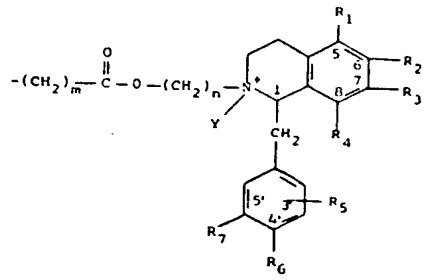
CLAIMS

1. A compound of the formula:



(I)

where B and C are each



where m is 2, 3 or 4, C is *para* or *meta* to B, n is 2, 3 or 4, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are the same or different and are each hydrogen or alkoxy of 1 to 4 carbon atoms, Y is lower alkyl of 1 to 4 carbon atoms, and X is a pharmaceutically acceptable anion, provided that at least one of R_1 to R_4 is lower alkoxy and at least one of R_5 to R_7 is lower alkoxy.

2. A compound according to claim 1 wherein C is *meta* to B.

3. A compound according to claim 1 or 2 wherein m = 2, n = 3, Y is methyl, one or two of R_1 to R_4 are hydrogen and the others are methoxy and two or three of R_5 to R_7 are methoxy, and when two are methoxy, the other is hydrogen.

4. A compound according to claim 3 wherein m = 2, n = 3, Y is methyl, R_1 and R_4 are hydrogen, R_2 and R_3 are methoxy, and R_5 and R_6 and R_7 are methoxy at the 3, 4 and 5 position of the phenyl ring.

5. A compound according to claim 3 wherein m = 2, n = 3, Y is methyl, R_1 and R_4 are hydrogen, R_2 and R_3 are methoxy, R_5 and R_6 are methoxy, and R_7 is hydrogen.

6. A compound according to claim 3 where m = 2, n = 3, Y is methyl, R_1 is hydrogen, R_4 is hydrogen, R_5 and R_6 are methoxy, and R_7 is hydrogen or methoxy.

7. A compound according to any one of claims 1 to 6 wherein X is iodide, mesylate, tosylate, bromide, chloride, sulphate, phosphate, hydrogen phosphate, acetate or propionate.

8. Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *m*-phenylene-3,3′-dipropionate dichloride.

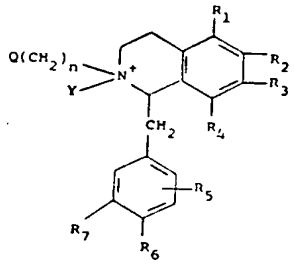
9. Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *m*-phenylene-3,3′-dipropionate dimesylate.

10. Bis-3-[N-methyl-1-(3,4-dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *p*-phenylene-3,3′-dipropionate.

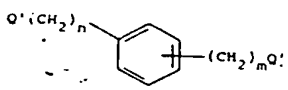
11. Bis-3-[N-methyl-1-(3,4,5-trimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinium] propyl *p*-phenylene-3,3′-dipropionate.

12. A method of preparing a compound as claimed in any one of claims 1 to 11 which comprises:

a) reacting a compound of formula:

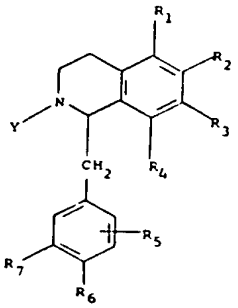


with a compound of formula:

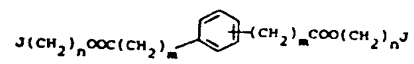


where n, m, Y and each of R_1 to R_7 have the same meaning as in claim 1 and Q and Q′ are functional atoms or groups which react together to form an ester linkage; or

b) quaternising a compound of formula:

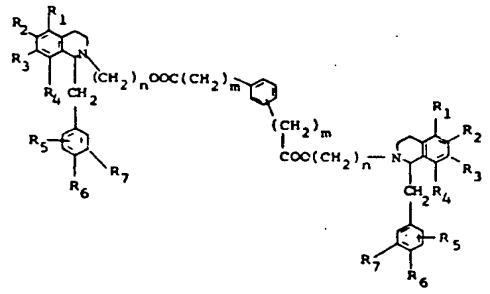


where Y and each of R_1 to R_7 have the same meaning as in claim 1 by reaction with a compound of formula:



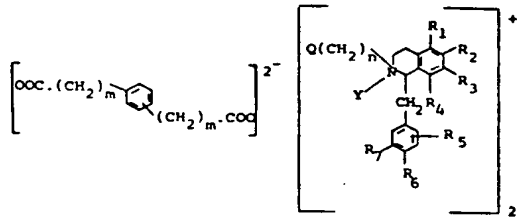
where J is halo and m and n have the same meaning as in claim 1; or

c) alkylating a ditertiary base of formula:



wherein n, m and each of R_1 to R_7 have the same meaning as in claim 1, or a corresponding monotertiary base where a group Y as defined in claim 1 is attached to one of the isoquinolinium nitrogen atoms, by reaction with an appropriate alkylating agent for introducing one or two Y groups as appropriate.

13. A method according to claim 12(a) which comprises rearrangement of a salt of formula



wherein each of m, n, Y and R_1 to R_7 have the same meaning as in claim 1 and Q is halo.

14. A method according to claim 12 or 13 wherein Q is chloro, bromo or iodo.

15. A method according to claim 12(a), 13 or 14 wherein the salt is heated.

16. A method according to claim 15 wherein the salt is heated to from 90° to 140°C.

17. A method according to any one of claims 12 to 16 wherein Q' is a silver carboxylate radical and Q is a halogen.

18. A method according to claim 17 wherein the halogen is bromine.

19. A method according to claim 12(a) wherein Q is hydroxy and Q' is carboxyl or a reactive derivative thereof.

20. A method according to claim 19 wherein the reactive derivative is an acid halide.

21. A method according to claim 20 wherein the reactive derivative is the acid chloride.

22. A method according to claims 19, 20 or 21 wherein an inert solvent is used.

23. A method according to claim 12(b) wherein J is iodo.

24. A method according to claim 12(b) or 23 wherein an inert solvent is used.

25. A method according to claim 24 wherein the reactants are heated to the reflux temperature of the reaction medium.

26. A method according to claim 12(c) wherein the alkylating agent used is a reactive ester derivative of an alcohol YOH.

27. A method according to claim 26 wherein the alkylating agent is an alkyl halide.

28. A method according to claim 27 wherein the alkylating agent is an alkyl bromide, alkyl chloride or alkyl iodide.

29. A method according to any of claims 12(c), 26, 27 or 28, wherein an inert solvent is used.

30. A method according to claim 29 wherein the reactants are heated up to the reflux temperature of the reaction mixture.

31. A method according to claim 12 substantially as hereinbefore described.

32. A compound as claimed in claim 1 when prepared by a process as claimed in any of claims 12 to 31.

33. A sealed container containing a compound as claimed in any one of claims 1 to 11 or 32 as a powder.

34. The container of claim 33 containing 10 to 400 mg of said powder.

35. A pharmaceutical composition for parenteral administration comprising a compound as claimed in any one of claims 1 to 11 or 32 and a pharmaceutically acceptable carrier therefor.

36. A composition as claimed in claim 35 in the form of a sterile solution, suspension or emulsion.

37. A composition as claimed in claim 35 in the form of an aqueous infusion fluid.

38. A composition as claimed in claim 35, 36 or 37 in the form of a unit dose.

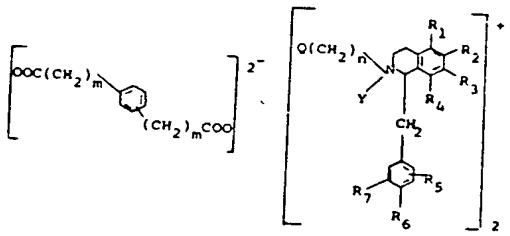
39. A composition as claimed in any of claims 35 to 38 or a container as claimed in claim 33 or 34

containing at least one bacteriostat, antioxidant, buffering agent, thickening agent or suspending agent.

40. A pharmaceutical composition as claimed in claim 35 substantially as described herein.

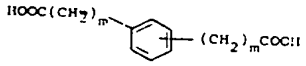
41. The use of a compound as claimed in any one of claims 1 to 11 or 32 as a neuromuscular blocking agent.

42. A salt of formula



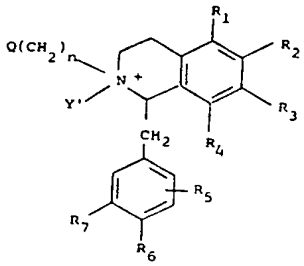
wherein each of n, m, Y and R_1 to R_7 has the same meaning as in claim 1 and Q is halo.

43. An acid of formula



wherein m is 2, 3 or 4 or an acid halide thereof.

44. A compound of formula



wherein each of R_1 to R_7 has the same meaning as in claim 1, Q is hydroxy or halo and Y' is hydrogen or alkyl of 1 to 4 carbon atoms.

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